# Less is more? Gene switch for healthy aging found

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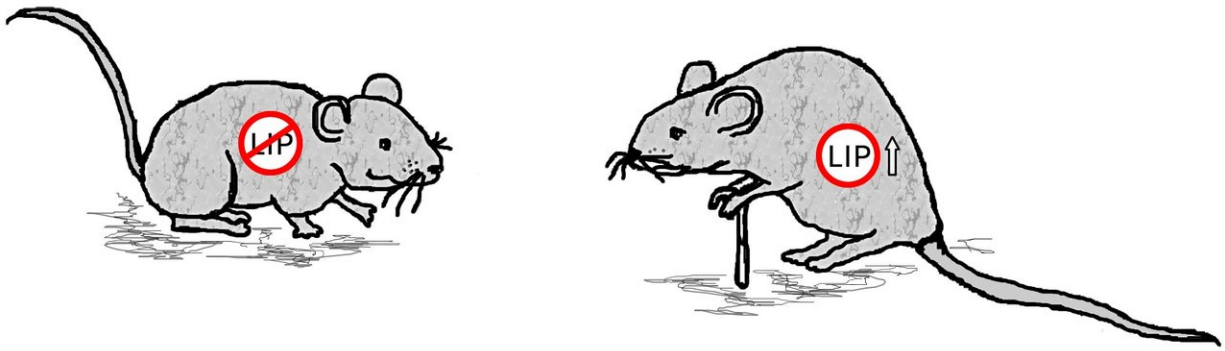


The C/EBPß-LIP gene regulator is involved in the aging process. If LIP is missing, the lifespan of mice increases and physical fitness is maintained during aging; without a calorie restriction. Credit: Kerstin Wagner / FLI

Aging is a major risk factor for physical frailty and the development of age-related diseases such as cancer, cardiovascular diseases, type II diabetes and Alzheimer's disease. Numerous studies have already shown that a calorie-restricted diet can significantly delay age-related conditions in several organisms like flies, worms, fish and mice, and that it even improves fitness at old age. But who wants to be on a lifetime diet?

Therefor it is important to clarify how a change in calorie intake affects

health during aging and which genes play a role in this process. With this knowledge, it may be possible to find new therapeutic approaches that can delay aging and age-related diseases.

In an earlier project the researchers from the European Research Institute for the Biology of Ageing (ERIBA) in Groningen, Netherlands, and the Leibniz Institute on Aging (FLI) in Jena, Germany, have shown how the protein complex mTORC1 uses the gene switch C/EBPß to control the metabolism of mice: C/EBPß can occur in a short variant (LIP) and a long variant (LAP). A high activity of mTORC1 leads to an increased formation of the short (LIP) variant.

The activity of mTORC1 is regulated by food intake and can be significantly reduced by a calorie-restricted diet, which in turn inhibits the formation of LIP. If the production of the short LIP variant is permanently suppressed in a mouse strain developed by the researchers, the result is a healthier metabolism with reduced body weight and improved insulin sensitivity. These LIP-reduced knockin mice showed improved metabolic health, similar to mice under calorie restriction, although the LIP-reduced mice were not on such a diet.

## Improving fitness in old age?

Based on these results, the researchers now examined whether the loss of LIP also results in an improvement in fitness in old age, similar to a diet. "The LIP-reduced mice are leaner at old age, they are able to cope better with changes in blood sugar levels, have a younger immune system, are significantly fitter and have a better motor coordination", says Prof. Cornelis Calkhoven, former research group leader at the FLI and now at ERIBA, summarizing the most important results of the new study.

In addition, LIP-reduced mice developed less cancer later in life than control mice. "We show that the female mice lived about 20% longer

without LIP than mice in the control group", adds Dr. Christine Müller from ERIBA; an indication that the loss of LIP can extend lifespan.

Although male mice with no LIP didn't show an increased lifespan, some of the age-related conditions were also less pronounced in the males. "If we find therapeutic ways to lower LIP levels in the body or to prohibit the effects of LIP, we may be able to delay the development of age-related diseases in the future", emphasizes Dr. Müller, "without the constraints that are associated with a diet."

## Do only women benefit from such intervention?

"This is hard to say, as our results are based on a specific knockin mouse strain", says Dr. Calkhoven about the research results. Other studies about calorie restriction also show differences between males and females that are not fully understood yet. "Therefore we have to continue our research in order to better understand the gender differences we have observed." Nevertheless, this study shows that by reducing LIP or inhibiting its function a potentially new approach has been found to prevent the onset of age-related diseases or slow down the aging process.

**More information:** Christine Müller et al. Reduced expression of C/EBPβ-LIP extends health- and lifespan in mice, *eLife* (2018). DOI: 10.7554/eLife.34985

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